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Key Words

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Ethical Statement

Full written consent to publication of this case has been given by next-of-kin. The authors are most grateful to a close family member to grant consent.

Contributorship Statement

Daniel Kirschenbaum: Dr. Kirschenbaum performed the neuropathological autopsy, drafted the initial manuscript, arranged the photodocumentation, and approved the final manuscript as submitted.

Carola Hedberg-Oldfors: Dr. Hedberg-Oldfors performed the genetic investigation and approved the final manuscript as submitted.

Anders Oldfors: Prof. Oldfors performed and supervised the genetic investigation, reviewed the manuscript, and approved the final manuscript as submitted.

Eduard Scherer: Dr. Scherer had followed the Proband's clinical course, provided his clinical neurological expertise, reviewed the manuscript, and approved the final manuscript as submitted.

Herbert Budka: Prof. Budka performed and supervised the neuropathology examination, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

The syndrome of sensory ataxic neuropathy with dysarthria and ophthalmoplegia (SANDO), defined genetically by mutations of the gene for the mitochondrial DNA polymerase-γ, *POLG*, was first described in 1997 (1). Since then, several case reports with various *POLG,* or more rarely *PEO1*, mutations have been published (2-4), some specifically addressing muscle and nerve pathology (1, 3), nerve electrophysiology (5), or radiological aspects (4, 6, 7). At the molecular level, A467T and W748S *POLG* mutations were described in SANDO by Tzoulis and others (2-4).

Patients with the A467T mutation show various clinical phenotypes, ranging from lethal Alpers-Huttenlocher syndrome to relatively mild SANDO (3, 6). However, since SANDO syndrome is a relatively recently recognised and rare entity, no description of CNS pathology has been made until now. On magnetic resonance imaging of the brain, involvement was evidenced by inferior olivary hypertrophy and cerebellar atrophy (6).

Comprehensive investigation of hypertrophy of the inferior olive showed that this process is almost exclusively secondary to deafferentation (8). This can occur at any site along the descending bisynaptic projection of the dentate nucleus to the inferior olive, also referred to as the Guillain - Mollaret triangle (9). Inferior olivary hypertrophy corresponds either to a lesion in the contralateral dentate nucleus or in the dentato-rubral projection before the fibres cross in the superior medullary velum. Alternatively, inferior olivary hypertrophy may be caused by an ipsilateral lesion in the already crossed dentato-rubral fibres, in the ipsilateral red nucleus, or the rubro-olivary projections in the central tegmental tract.

Here we present the first neuropathological documentation of cerebral changes in a patient with SANDO syndrome, thus enabling identification of the neuronal target regions of the genetic defect.

This is the case of a 50 year-old female who presented with symptoms in her early twenties, when she noted impaired sensation in her feet on the pedals while driving. Subsequently, in her late thirties, she developed severe symmetrical sensory axonal neuropathy associated with frequent falls. Electroneurographical tests showed loss or pronounced amplitude reduction of sensory action potentials, while motor neurography was normal. Hence, the results were interpreted as pronounced axonal sensory polyneuropathy. In addition, horizontal and upward gaze palsy became

apparent. As the disease progressed, the patient developed diplopia, ptosis and dysarthria, pointing ataxia with pseudoathetosis, severe gait ataxia and dysaesthesia. The patient died suddenly of a cardiac arrest at the age of 50. Of note, the autopsy did not show any specific pathology in the cardio-pulmonary system.

During the protracted course of the disease, laboratory tests (vitamins E and B12, anti-ganglioside antibodies, anti-Hu, -Ri, -Yo antibodies, phytanic acid, beta lipoproteins) were not diagnostic. Similarly, the cerebrospinal fluid showed, on one occasion, slightly elevated non-specific protein levels (0.62 g/L) and no oligoclonal bands. Early in the disease course, magnetic resonance imaging of the brain and spinal cord was normal, later the patient refused imaging. A sural nerve biopsy showed extensive loss of myelinated and non-myelinated axons accompanied by fibrosis. No inflammation or amyloid deposition were seen. The patient did not agree to a muscle biopsy (in retrospect, it might have shown COX negative and ragged red fibres). The mother and two sisters were healthy. Genetic tests for Charcot – Marie – Tooth 1a, Friedreich's ataxia, spinocerebellar ataxia 1 and 3, Huntington's disease and dentatorubro-pallidoluysian atrophy were all negative. Therapeutic trials with intravenous immunoglobulins proved to be ineffective. A CANOMAD syndrome (chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins, disialosyl antibodies) was considered: however, no corresponding anti-ganglioside antibodies were found. SANDO syndrome was also considered, but no genetic testing was done *ante mortem*.

For neuropathology, only the brain but not the spinal cord or muscle were available. The formalin-fixed brain weighed 1268g. On gross inspection, the hemispheres were symmetrical and there was no evidence of atrophy or focal lesions. Significant macroscopic findings were localized to the brainstem and included protruding inferior

olives and pallor of the substantia nigra. Microscopically, pronounced gliosis and neuronal loss affected multiple neuroanatomical sites (Fig.1). Both inferior olives were remarkably prominent when examining the brainstem macroscopically *in toto* and on histological sections (Fig.1 A, B, C). Striking microscopic changes were apparent in the inferior olives, where the ventral sections of the principal part showed marked gliotic change with gemistocytes and neuronal loss (Fig.1 D, F). The remaining neurones showed characteristic changes of inferior olivary hypertrophy (8) such as swollen rounded neurones with cytoplasmic vacuoles and plump dendritic processes (Fig.1 E). There was no apparent degeneration in the spinothalamic tract. In the posterior column – medial lemniscus pathway, the fasciculus gracilis showed pallor in both the HE and Luxol-PAS stains. More cranially in the brainstem and above, the medial lemniscus showed no obvious degeneration. The cerebellar cortex showed focal Purkinje cell loss accompanied by Bergmann gliosis (Fig. 1 G). In sections of midbrain, the substantia nigra, red nucleus and locus coeruleus showed pronounced nerve cell loss, astrogliosis and microgliosis. Similar degenerative changes were also observed in the dentate nucleus. In the substantia nigra, neuronal loss was most apparent in the pars compacta, where pigmented cells were scarce and free pigment clumps were disseminated in the parenchyma intermingled with prominent astrocytes (Fig. 1 H). A GFAP stain showed gliosis also in the pars reticulata. In the thalamus, the most pronounced gliotic change, as highlighted by immunohistochemistry for GFAP, was apparent in the lateral aspects of the ventral posterolateral nucleus (VPL). This pronounced gliotic change involved multiple structures in a stripe-like pattern. This gliotic stripe descended from the lateral-posterior nucleus through the central and medial aspects of the VPLa. From there it ran along the lateral part of the VPLp and inferior VPLa, until and involving the ventral posteroinferior nucleus and the zona incerta. There, the stripe-like gliosis

sharply turned laterally through the ventromedial basal nucleus and ended in the lateral parts of the centromedian nucleus. Additionally, paraventricular parts of the anterior and mediodorsal (MD) nuclei were strongly affected. The MD was otherwise relatively spared except some foci of stronger gliosis. There was no cortical involvement; however, the lentiform nuclei showed neuronal loss and gliosis (Fig.1 J). Vacuolar change of gray matter was absent.

Mutation analysis of *POLG* (NM_002693.2) was performed by Sanger sequencing and revealed heterozygosity for two missense variants. One was the c.1399G>A p.A467T and the second was the c.2243G>C p.W748S, both previously described in patients with SANDO syndrome (2-4).

This is the first documentation of central neuropathological features in a patient with genetically confirmed SANDO syndrome. Our results demonstrate a pronounced multisystem degeneration with most extensive changes in rhombencephalic and mesencephalic structures, followed by less severe changes in the basal ganglia and thalamus. Specifically, degenerative changes were found within the dentate and red nuclei corresponding to the Guillain – Mollaret triangle, which caused the striking bilateral hypertrophy of the inferior olives. These pathological findings are in line with prior brain-imaging studies (4, 6, 7, 9) and the clinical manifestations of pronounced cerebellar ataxia. In the current case, imaging was declined by the patient in the further disease course, thus actual pathological correlation of imaging findings could not be provided. While inferior olivary hypertrophy follows most frequently cerebrovascular or posttraumatic lesions, or brain stem tumors (8, 9) and may manifest as palatal tremor (7, 10) that was not reported in our patient, symmetrical inferior olivary hypertrophy is rare. However, imaging studies showed that bilateral inferior olivary hypertrophy is a common feature in patients with *POLG* mutations (6).

In summary, this adult case of SANDO syndrome features a distinctive brain pathology that expands the spectrum of mitochondrial encephalopathies. The present report provides the basis for future studies on *POLG* mutations that might help to better understand the selective vulnerability of affected brain structures.

References

1. Fadic R, Russell JA, Vedanarayanan VV, Lehar M, Kuncl RW, Johns DR. Sensory ataxic neuropathy as the presenting feature of a novel mitochondrial disease. Neurology 1997; 49 (1): 239-245

2. Hanisch F, Kornhuber M, Alston CL, Taylor RW, Deschauer M, Zierz S. SANDO syndrome in a cohort of 107 patients with CPEO and mitochondrial DNA deletions. J Neurol Neurosurg Psychiatry 2015; 86 (6): 630-634

3. Rajakulendran S, Pitceathly RD, Taanman JW, Costello H, Sweeney MG, Woodward CE, Jaunmuktane Z, Holton JL, Jacques TS, Harding BN, Fratter C, Hanna MG, Rahman S. A Clinical, Neuropathological and Genetic Study of Homozygous A467T POLG-Related Mitochondrial Disease. PLoS One 2016; 11 (1): e0145500

4. Tzoulis C, Engelsen BA, Telstad W, Aasly J, Zeviani M, Winterthun S, Ferrari G, Aarseth JH, Bindoff, LA. The spectrum of clinical disease caused by the A467T and W748S POLG mutations: a study of 26 cases. Brain 2006; 129 (Pt 7): 1685-1692

5. Lehmann D, Kornhuber ME, Clajus C, Alston CL, Wienke A, Deschauer M, Taylor RW, Zierz S. Peripheral neuropathy in patients with CPEO associated with single and multiple mtDNA deletions. Neurology: Genetics 2016; 2 (6): e113

6. Kinghorn KJ, Kaliakatsos M, Blakely EL, Taylor RW, Rich P, Clarke A, Omer S. Hypertrophic olivary degeneration on magnetic resonance imaging in mitochondrial syndromes associated with POLG and SURF1 mutations. J Neurol 2013; 260 (1): 3-9

7. Johansen KK, Bindoff LA, Rydland J, Aasly JO. Palatal tremor and facial dyskinesia in a patient with POLG1 mutation. Mov Disord 2008; 23 (11): 1624-1626

8. Jellinger K. Hypertrophy of the inferior olives. Report on 29 cases. Z Neurol 1973; 205 (2): 153-174

9. Sanverdi SE, Oguz KK, Haliloglu G. Hypertrophic olivary degeneration in children: four new cases and a review of the literature with an emphasis on the MRI findings. Brit J Radiol 2012; 85 (1013): 511-516

10. Zadikoff C, Lang AE, Klein C. The 'essentials' of essential palatal tremor: a reappraisal of the nosology. Brain 2006; 129 (Pt 4): 832-840

Figure caption

Figure 1. Cerebral pathology in SANDO syndrome. Symmetrical hypertrophy of the inferior olives was striking macroscopically *in toto* (A, arrows), on coronal slices (B) and on histological sections (C). Microscopically the inferior olives showed gemistocytic gliosis (D) and neuronal swelling with cytoplasmic vacuoles and plump dendritic processes (E). Prominent gliosis throughout the inferior olives was also seen (F), as well as Bergmann gliosis of the cerebellar vermis (G). Further gliotic changes were seen in the substantia nigra (H) and in the red nucleus of the mesencephalon (I). Subcortically, profound affection of the caudate nucleus (J) and thalamus (K) was seen. Sections were stained with Luxol fast blue-Nissl (C), hematoxilin eosin (D, H); immunohistochemistry against neurofilaments 70 and 200 kDa (E) and glial fibrillary acidic protein (F, G, I, J, K). Scale bars are 10 mm (A, B), 4 mm (C), 75 µm (D), 30 µm (E), 500 µm (F, G), 200 µm (I, K), 100 µm (H, J).